

Immunoadsorption in Patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy with Unsatisfactory Response to First-Line Treatment

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Key Words

Immunomodulatory treatment • INCAT score • Intravenous immunoglobulin • Tryptophan immunoadsorption

Abstract

Background/Aims: First-line treatment options for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are corticosteroids, intravenous immunoglobulin, and plasma exchange. In a significant number of patients, first-line therapy fails, and long-term maintenance treatment still remains a therapeutic challenge. Immunoadsorption (IA) may be an alternative to classical plasma exchange in the therapy of immune-mediated neurologic diseases. The aim of this investigation was to evaluate efficacy and safety of IA in patients with CIDP with unsatisfactory response to first-line treatment options. **Methods:** CIDP patients received adjunct IA treatment using tryptophan-immune adsorbers. The inflammatory neuropathy cause and treatment disability (IN-CAT) score was used to grade disability and monitor treatment effects. **Results:** In total, 14 CIDP patients were analyzed. Ten patients were treated in hospital. After one IA

treatment series, the INCAT score decreased significantly in all 10 patients. Four of these 14 patients were treated in outpatient clinics using long-term maintenance IA with 1–2 treatments per week. In these 4 patients, effects of long-term maintenance IA resulted in an improvement of overall disability. In all patients, IA was safe, well tolerated, and no severe adverse effects occurred. **Conclusion:** IA could be an effective and safe option for CIDP patients with unsatisfactory response to first-line treatment options and for long-term maintenance treatment.

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Introduction

First observations of recurrent corticosteroid-responsive polyneuropathies led to the definition of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as an immune-mediated disorder in 1958 [1, 2]. CIDP thus is a relatively new entity which has been differentiated from the acute form, known as Guillain-Barré syndrome (GBS) which was first described in 1916 [3].

The classic presentation is characterized by progressive or relapsing symmetrical motor or sensory symptoms, developing over more than 2 months, elevated cerebrospinal fluid (CSF) protein levels and heterogeneous slowing of nerve conduction velocities. In addition to the classic presentation, a spectrum of CIDP variants exists, with distribution of symptoms including predominantly distal forms, asymmetric, multifocal, and pure sensory forms [4]. CIDP is associated with substantial morbidity and even mortality. Although defined diagnostic criteria for CIDP are meanwhile increasingly sensitive and specific [5–7], there is still significant overlap between CIDP and other neuropathies, sometimes leading to underdiagnosis of the disorder. The estimated prevalence for the disease varies from 1 to 8.9 per 100,000; the reported incidence rate is 1.6/100,000/year [8–10].

The pathogenesis of CIDP still remains to be fully elucidated; however, it is generally accepted that CIDP is an immune-mediated disorder with dysfunctions on the humoral and cellular level [11]. Cell-mediated and humoral immune responses directed against peripheral nerve antigens cause organ-specific damage, which is a classical feature of an autoimmune disease. Passive transfer experiments have revealed that serum or purified immunoglobulin G from CIDP patients can induce marked conduction block and demyelination in rat nerves thus supporting the importance of antibodies in the pathogenesis [12]. Myelin protein zero, gangliosides, and related glycolipids have been identified as putative target antigens [4].

Early and effective treatment of CIDP is important to minimize or prevent axonal degeneration, which occurs secondary to demyelination. Responses to immunomodulation with corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange (PE) have been confirmed in trials, suggesting no difference in efficacy among these three therapies in reducing impairment at least temporarily [7, 13–17]. If there is no response to these three first-line therapeutic options, which occurs in 20–40% of patients, switching between treatments can increase the overall number of responders considerably [4, 13]. If the response is inadequate or maintenance doses of the initial treatment are high, combination of treatments should be considered as well as adding an immunosuppressant or immunomodulatory drug [18–20]. According to current guidelines, treatment must be continued in responding patients until maximum improvement or stabilization occurs [20]. Long-term maintenance treatment still remains a challenge. Both PE and IVIG are possible long-term treatments usually in combination with immunosuppressive drugs [21, 22].

Selective immunoadsorption (IA) seems to be an equivalent alternative to classical PE in several neuroimmunological diseases, e.g. GBS and myasthenia gravis [23–29] due to its similar efficacy and advantageous safety profile avoiding substitution of human plasma products. However, a randomized clinical trial comparing these treatment options is currently not available. Although there are no direct comparisons between PE and IA in patients with CIDP, studies comparing the two treatments have been conducted in glomerulonephritis [30]. Immediate antibody elimination, pulsed induction of antibody redistribution, and immunomodulation are major mechanisms of action [31]. Using PE, plasma is separated from blood cells, discarded and substituted by a human albumin solution or fresh frozen plasma. In the case of IA, however, plasma is passed through an adsorber column after plasma separation, and the treated plasma is then returned to the patient. With the tryptophan-linked polyvinylalcohol IA system, immunoglobulins including IgG and IgM and immune complexes are eliminated from the plasma by hydrophobic and ionic interaction with the adsorber surface [27, 32]. Tagawa et al. [33] revealed that the tryptophan-linked column very effectively removes anti-ganglioside immunoglobulin G antibodies from plasma.

The aim of this retrospective investigation was to evaluate the efficacy and safety of IA in patients with CIDP with unsatisfactory response to first-line treatment options as well as a possible long-term treatment option for patients with a relapsing and chronic progressive course, which has not been evaluated yet.

Material and Methods

In order to assess safety and efficacy of IA as a therapeutic option in CIDP patients with unsatisfactory response to first-line treatment options (i.e. corticosteroids, IVIG, or PE), we performed a retrospective analysis of CIDP patients, who were treated in four centers. Unsatisfactory response to at least two of these first-line treatment options was defined as (a) when first-line treatment options were clinically not effective, (b) maintenance doses of the initial treatment were high, (c) or unfavorable side effects occurred. Additionally, a further criterion was adding of an immunosuppressant medication (e.g. azathioprine in combination with corticosteroids or azathioprine alone) as maintenance therapy to achieve an improvement of symptoms related to CIDP.

To confirm the diagnosis of definite CIDP, clinical symptoms, course of the disease, CSF compositions, and neurophysiological findings according to the current diagnostic guidelines were evaluated in all patients [18, 20, 34, 35]. Patients with pure motor syndromes were excluded. Patients with CSF cell counts of more than

Table 1. The INCAT disability scale, modified from Hughes [36]

Arm disability	Leg disability
0 No upper limb problems	0 Walking not affected
1 Symptoms in 1 arm or both arms not affecting ability to perform any of the following functions: doing all zippers and buttons, washing or brushing hair, using knife and fork together, handling small coins	1 Walking affected, but walks independently outdoors
2 Symptoms in 1 arm or both arms, affecting but not preventing any of functions listed above	2 Usually uses unilateral support (stick, single crutch, 1 arm) to walk outdoors
3 Symptoms in 1 arm or both arms, preventing 1 or 2 of functions listed above	3 Usually uses bilateral support (sticks, crutches, frame, 2 arms) to walk outdoors
4 Symptoms in 1 arm or both arms, preventing 3 or all of functions listed above, but some purposeful movements still possible	4 Usually uses wheelchair to travel outdoors, but able to stand and walk few steps
5 Inability to use either arm for any purposeful movement	5 Restricted to wheelchair, unable to stand and walk few steps with help

20 cells/ μ l were considered to be suffering from an infectious polyneuropathy and therefore excluded. Neurophysiological testing was routinely performed in all patients, which included electromyographic as well as electroneurographic testing for determination of the nerve conduction velocity (NCV). Patients without any NCV changes or conduction blocks were excluded.

IA was performed as adjunctive therapy when patients fulfilled the latter criteria using the tryptophan-linked polyvinyl alcohol adsorber TR-350, after membrane plasma separation with the polyethylene plasma separator OP-05W (Asahi Kasei Kuraray Tokyo, Japan), and in combination with the Octo Nova extracorporeal circuit technology (SW 4.30.2, front 4.30.0; Diamed Medizintechnik, Cologne, Germany). Adsorber, plasma separator, and tubing system were for single use only. Vascular access was achieved in patients, who were treated in hospital by placement of a double lumen central venous catheter in the jugular or subclavian vein.

According to the protocol of the Department of Nephrology of the University of Cologne, for all in-hospital IA treatments, a plasma treatment volume for tryptophan IA of 4 l was implemented. This was achieved in practice by sequential use of two TR-350 IA columns. Frequency of IA was individually adjusted according to clinical signs and fibrinogen levels. If necessary, treatment intervals were extended depending on the degree of fibrinogen depletion, which is caused by adsorber treatment. As assessed by post-IA measurement of fibrinogen levels, a substitution of fibrinogen was not necessary for any patient.

In long-term outpatient patients, peripheral venous access ($n = 1$) or arteriovenous shunt ($n = 3$) was used. In general, the plasma treatment volume for tryptophan IA is 2.0–2.5 l, which was used for all long-term outpatient treatments.

Response to treatment was measured by improvement in strength, sensation and ability to perform activities of daily living. Functional disability was assessed with the inflammatory neuropathy cause and treatment disability (INCAT) score [36] (see table 1).

Statistical analysis was performed using SigmaStat software (SigmaStat Version 3.0, SPSS Inc., Chicago, Ill., USA). The Wilcoxon signed-rank test was used for the analysis of change in INCAT score from baseline to time after IA, because variables could not be assumed to be normally distributed. Descriptive statistics are provided as mean and standard deviation.

Results

We identified 14 patients with CIDP (mean age 56 ± 15 years; 6 women, 8 men) and unsatisfactory response to at least two first-line treatment options. Ten patients were treated in-hospital. Four of these 14 patients were treated in outpatient clinics using long-term maintenance IA with 1–2 treatments per week.

The course of the disease revealed that a remitting or chronic progressive course was present with a nadir of disease beyond 4 weeks, differentiating acute demyelinating polyradiculoneuropathy (GBS) from CIDP. Clinical findings were compatible with progressive or relapsing motor and sensory dysfunction of more than one limb. CSF examinations were performed in all patients; an elevated cell count in the CSF was not observed. Disseminated NCV reduction or conduction blocks were present in all cases. Electromyographic findings with pathological spontaneous activity and neurogenic action potential alterations were found in all patients. Following establishment of the diagnosis CIDP, all patients were treated with corticosteroids, IVIG, or PE as first-line treatment. In all patients, the first-line treatment was clinically not

Table 2. Clinical characteristics of CIDP patients with unsatisfactory response to first-line treatment options treated in hospital with IA

Patient No.	Age at diagnosis years	Time between diagnosis and start of IA, years	Number of IA per series	Number of series	INCAT score at baseline	INCAT score after IA	Other treatments before start with IA	Maintenance treatment with corticosteroids and azathioprine	Maintenance treatment with azathioprine alone
1	53	4	3	8	6	5	IVIG, CS, PE	–	+
2	58	1	3	7	4	3	IVIG, CS	+	–
3	68	4	3	3	6	5	IVIG, CS, PE	+	–
4	67	2	3	3	2	1	IVIG, CS	*	–
5	54	7	3/5	2	5	4	IVIG, CS, PE	+	–
6	47	<1	5	1	8	7	IVIG, CS	+	–
7	69	5	4	1	6	4	IVIG, CS	+	–
8	72	<1	4	1	5	4	IVIG, CS	+	–
9	75	<1	4	1	7	6	IVIG, CS	–	–
10	70	<1	3	1	8	8	IVIG, CS	*	–
Mean	63		3.6	2.8	5.7	4.7			
SD	10		0.7	2.6	1.8	2.0			
Median	68		3.5	1.5	6.0	4.5			

CS = Corticosteroids; IVIG = intravenous immunoglobulin; PE = plasma exchange. Asterisk signifies CS alone.

effective, maintenance doses of the initial treatment were high, or unfavorable side effects occurred.

Ten CIDP patients with unsatisfactory response to first-line treatment options received in-hospital IA treatment in a single center between 1999 and 2009. Five of these patients received one series with a mean of 4.0 ± 0.7 IA treatment sessions with a treatment volume of 4 l plasma per session within less than 14 days. The other 5 patients received repeated series (range of 2–8 series, mean 4.6 ± 2.7 series) within 1–5 years. In patients with more than one IA series, the series comprised 3–5 IA treatment sessions (mean of 3.2 ± 0.5). The total number of IA per patient ranged between 8 and 24 treatment sessions. After one IA treatment series, the INCAT score decreased significantly from 5.7 ± 1.8 to 4.7 ± 2.0 ($p = 0.004$; Wilcoxon-signed rank test) in all 10 patients. In patients who received one series of IA treatment ($n = 5$), clinical improvement persisted within a range from 4–8 weeks. All but one patient improved one or more points on the INCAT scale, which represented a clinically meaningful change in disability (see table 2).

In the vast majority of these patients who were treated in hospital, adding of an immunosuppressant medication to corticosteroids (predominantly prednisolone) as long-term maintenance treatment to improve clinical symptoms related to CIDP was necessary during the course of the disease (see table 2). The mean corticosteroid dosage

was 19 ± 17 mg/day (range 10–50 mg), for azathioprine 117 ± 56 mg/day (range 50–150 mg).

Four patients were treated in outpatient clinics using long-term IA with one ($n = 3$) or two ($n = 1$) treatments per week (see table 3). Extension of intervals between IA treatments was attempted in all patients, but led to deterioration of the clinical status (e.g. muscle weakness). Three of these 4 patients had been treated with PE prior to IA. In one of these patients, PE was discontinued due to unfavorable side effects (i.e. severe fatigue). To avoid repeated substitutions with human blood products, PE was replaced by IA in 2 patients. In all patients, long-term IA treatment effects resulted in improvement of overall disability. The INCAT score improved under long-term IA in all 4 patients within a range of 1–7 points. During long-term IA treatment, the dose of immunosuppressive drugs could be reduced in these 4 patients.

In all patients, IA was safe and well tolerated, and no severe side effects occurred. No adverse event occurred which necessitated termination of treatment. Allergic reactions were not observed.

Discussion

In our retrospective analysis, we identified 14 CIDP patients with unsatisfactory response to first-line treatment options. Ten of these patients were treated with one

Table 3. Clinical characteristics of CIDP patients with unsatisfactory response to first-line treatment options treated with long-term IA in outpatient clinics

Patient No.	Age at diagnosis years	Time between diagnosis and start of IA, years	Number of IA per week	INCAT score at baseline before IA	INCAT score under long-term IA	Other treatments before start with IA	Clinical outcome after IA
11	27	11	1	7	6	CS, IVIG, methotrexate, PE	Improvement in strength, reduction in overall disability
12	31	1	2	10	5	CS, IVIG, cyclophosphamide, azathioprine, PE	Improvement from tetraparesis and wheelchair dependency to ability to walk, improvement in strength
13	60	3	1	8	1	CS, IVIG, cyclophosphamide, azathioprine	Improvement from wheelchair dependency to ability to walk, improvement in strength
14	35	3	1	4	1	CS, IVIG, cyclophosphamide, PE	Improvement in walking distance, significant improvement in strength of arms and legs

or more IA treatment series. All but one patient improved in the INCAT score by at least one point. The patient who did not change had the highest INCAT score suggesting a high degree of associated axonal loss, which could have influenced the prognosis in this patient.

Furthermore, we identified 4 patients who had been treated with long-term IA in outpatient clinics. In these patients, frequency of long-term IA varied from one to two applications per week. During long-term IA, the clinical status improved in all patients without adverse effects. Before initiating IA, 3 of these 4 patients had been treated with PE. To avoid repeated substitutions with human blood products and due to severe side effects, PE was replaced by IA in these 3 patients. Preliminary data of a successful change from PE to IA in long-term treatment of CIDP had been reported previously [37]. Successful long-term outpatient treatment of another immune-mediated neurological disorder with IA has already been described in rare patients with severe refractory myasthenia gravis. In these patients, the number of myasthenic crises could be reduced by 89% per year by treatment with IA [28].

The increasing knowledge on the pathogenic relevance of autoantibodies contributes to the rationale for IA treatment, which selectively removes antibodies in plasma. The presence of autoantibodies against various proteins and glycolipids of the peripheral nerve in serum and CSF from CIDP patients supports the therapeutic value of IA. The tryptophan-immobilized column proved to adsorb anti-ganglioside immunoglobulin G antibodies

from plasma of patients with GBS and Miller-Fisher syndrome very effectively [33]. Therapeutic effects of PE and IA in autoantibody-mediated diseases can be attributed to three major mechanisms: immediate intravascular reduction of (auto)-antibody concentration, pulsed induction of antibody redistribution, and subsequent immunomodulatory changes [31].

To date, more documented experience has been reported with therapeutic use of PE worldwide. One reason is the fact that IA is not approved for clinical use in the USA and several other countries. In addition to regulatory approval, issues of reimbursement might prevent recent use of IA. In Germany, selective IA has been increasingly used in autoimmune-related neurological diseases due to its equivalent efficacy and advantageous safety profile [23]. It had been shown that IA is an effective treatment for GBS patients [23–25]. However, although IA therapy has been used as a treatment option for CIDP for a number of years, the efficacy of IA treatment for CIDP had not been analyzed in a larger number of patients yet, and only few case reports are found in the literature [38–40]. In a small pilot trial, safety and efficacy of selective IA were compared with IVIG [41]. Five CIDP patients receiving monthly 3 IA for 6 months showed a response rate of 80%. In contrast, IVIG-treated patients showed a response rate of 50%. Unfortunately, however, the study was not powered to detect a statistically significant difference between the treatment arms [41]. In contrast, results of our retrospective analysis suggest that IA could be an effective and safe option for CIDP patients

with unsatisfactory response to first-line treatment options and for long-term maintenance treatment.

In Germany, reimbursement of outpatient IA by statutory health insurances requires an individual application. The cost of IA treatment for hospitalized patients is about EUR 2,300 per treatment, adding up to EUR 6,900–11,500 for a treatment series of 3–5 IA [42]. The cost of outpatient IA treatment is essentially identical. In comparison, treatment with IVIG may have a higher cost [13, 43].

A shortcoming of our analysis is that the optimal IA treatment regimen for CIDP remains to be investigated systematically. For CIDP patients who were treated in hospital, 3–5 IA treatments with a predefined treatment volume of 4 l within less than 14 days had significant and clinically relevant efficacy. The number of IA treatments used correlates well with other autoimmune neuropathies. However, treatment volumes with the tryptophan adsorber were comparatively large in this study and cannot be taken as obligatory. In other autoimmune neuropathies including myasthenic crisis and GBS, PE and tryptophan IA were already effective with plasma treatment volumes of 1–2.5 l [24, 25, 27, 40, 44, 45]. In patients treated with long-term IA, a weekly treatment volume of 2.5 l

seems to be adequate. Therefore, the number of IA treatments as well as treatment volumes should be adjusted to individual patients' needs.

In conclusion, our study demonstrates that IA can be regarded as an effective and safe option for the treatment of CIDP patients with unsatisfactory response to first-line treatment options. Thus, IA should be considered for patients with unsatisfactory response to first-line treatment including IVIG. Long-term maintenance treatment with IA proves to be an effective outpatient treatment to stabilize neurologic status of rare CIDP patients with unsatisfactory response to first-line treatment options. However, further limitations of our investigation are the retrospective character and the lack of a control group; therefore, a larger prospective study is needed to validate our findings.

Disclosure Statement

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